REMARKS

Claim 25 is amended herein to correct a typographical error. This amendment does not add new matter as it is fully supported throughout the specification and in the claims as originally filed.

After amending the claims as set forth above, claims 1, 3, 10, 11, and 16-31 are now pending in this application. A detailed listing of all claims that are, or were, in the application, regardless of whether a particular claim remains under examination in the application, is presented, beginning on page 2 of this paper under "Listing of Claims," with an appropriate defined status identifier.

I. 35 U.S.C §112, First Paragraph (Written Description)

A. Claims 1, 3, and 25-31

The rejection of claims 1, 3, and 25-31 under 35 U.S.C §112, first paragraph for alleged lack of written description on the grounds that the amendments and new claims contained in the response mailed October 28, 2002 allegedly contained new matter is respectfully traversed. Applicants respectfully disagree with the Examiner's that the amendments contain new matter and cite support in the specification for same as described below.

Applicants have reviewed the Office Action dated February 3, 2003 in detail. Applicants' understanding of the Examiner's comments (pages 3-6) regarding the above referenced rejection is that the rejection is based upon the inclusion of the phrases "non-pathogenic bacterium comprising a nucleic acid molecule encoding said thiaminase" and "sufficiently to induce apoptosis" in the amended and new claims. In view of this understanding, Applicants will cite support for these phrases as they pertain to each of the rejected claims as follows.

With regard to claims 1, 3, 25 and dependent claims 26-31, which include the phrase "non-pathogenic bacterium," the Examiner asserts that the specification allegedly provides no

description of a non-pathogenic bacterium (Office Action, page 4). The Examiner also asserts that *Clostridium* and *Salmonella* are well known in the art to be pathogenic.

Applicants respectfully submit that, as described below, the strains of these bacteria in the preferred embodiments are *attenuated* or *genetically modified to be non-pathogenic*. The specification describes several non-pathogenic bacteria and cites reports from the literature in which they are employed in cancer therapy. For example, at page 34, lines 25-32, the specification cites a report in which "it was found (Pawelek et al, 1997) that attenuated (non-pathogenic), hyperinvasive, polyauxotrophic mutants of *S. typhimurium* targeted melanoma in mice, and *in vivo* reduce the rate of tumor growth" (emphasis added). Advantageous attributes of attenuated *Salmonella* are listed on page 35, lines 1-11. The specification also describes non-pathogenic strains of *Clostridium* (see, for example, page 36, line 3 to page 37, line 5), in particular, the specification states, "avirulent *C. beijerinckii* have been genetically engineered to express enzymes that would cleave prodrugs" and suggests using *C. beijerinckii* engineered to overexpress and secrete an appropriate thiaminase. Therefore, Applicants submit that the phrase "non-pathogenic bacterium" is fully described in the specification.

Claims 1, 3, and dependent claims 28-31 are directed to methods which include administration or delivery of, *inter alia*, a "non-pathogenic bacterium comprising a nucleic acid molecule encoding said thiaminase." The Examiner asserts that the specification allegedly lacks written description of "methods comprising administration of a non-pathogenic bacterium comprising a recombinant nucleic acid molecule encoding a thiaminase" (Office Action, page 5).

First, the Applicants respectfully note that the Examiner concedes that the specification indeed teaches the construction of a vector adapted for expression in prokaryotic cells such as *E. coli* although a variety of other bacteria can be used as well (Office Action, page 4). Second, the specification provides description of and cites reports of the use of non-pathogenic bacteria in cancer therapy. See, for example, "Example 6" at pages 33-37, in which a method in which thiaminase carried by non-pathogenic bacteria may be used in treating prostate cancer is discussed. Furthermore, an example of how to engineer an attenuated *Salmonella* strain to

express thiaminase for an anti-tumor therapy and its delivery is described (specification page 35, lines 12-18). Therefore, the teaching of the construction of a non-pathogenic bacterium comprising a nucleic acid encoding thiaminase, in conjunction with the examples in the specification and the reference to exemplary reports in the literature of the use of bacteria in the treatment of cancer, sufficiently describes the claimed methods in accordance with 35 U.S.C. § 112.

Finally, the Examiner asserts that claim 1 lacks sufficient written description support for methods for using a non-pathogenic bacterium comprising a recombinant nucleic acid encoding a thiaminase to induce apoptosis in vertebrate cells (Office Action, page 5). Applicants respectfully disagree with the Examiner's assertion. First, the specification teaches that thiaminase can induce apoptosis in vertebrate cells. See the specification at, for example, page 33, lines 30-32, which states "[t]he many cell lines in which the *Naegleria* agent (thiaminase I) was shown to induce apoptosis include two cell lines derived from human prostate cancers." Second, as described in the preceding paragraph of this paper, the specification provides description of non-pathogenic bacteria comprising nucleic acids encoding thiaminase. One of skill in the art would recognize that a bacterium expressing thiaminase could therefore induce apoptosis in vertebrate cells. Thus, the specification provides adequate support for claimed methods.

As detailed in the preceding paragraphs, Applicants have cited to support in the specification which sufficiently provide written description for the rejected claims 1, 3, and 25–31. Accordingly, Applicants respectfully request withdrawal of these rejections.

B. Claims 1, 3, 11, 18, 19, and 25-31

The rejection of claims 1, 3, 11, 18, 19, and 25-31 under 35 U.S.C. §112, first paragraph as containing subject matter that was allegedly not described in such a way as to convey to one of skill in the art that Applicants had possession of the claimed invention, is respectfully traversed.

The Examiner asserts that the specification allegedly fails to satisfy the written description requirement with regard to the claimed nucleic acid sequences encoding thiaminases or derivatives thereof isolated from species other than *N. gruberi* (Office Action, page 8). Applicants respectfully disagree with the Examiner's assertion and respectfully submit that the specification fully satisfies the written description requirement with reference to structural properties of thiaminase. First, the amino acid sequences of thiaminase from *Naegleria gruberi* and *Bacillus thiaminolyticus* are presented in Figure 5 and Figure 8, respectively. Second, at least two other structural properties are described, in particular, "the catalytic domain segment of 13 residues surrounding the active site Cys, VYGFPQYLCSNFL" and " the six amino acid sequence GYSESM that starts at residue 228 of Naegleria thiaminase I (Figure 7) ... [which] is part of the pyrimidine coordinate residues" (page 29, line 17 to page 30, line 2). Given the two exemplary thiaminase sequences and the structural motifs described above, one of skill in the art could readily find analogous sequences in any public database using standard sequence analysis tools (*e.g.*, BLAST).

The Examiner further asserts that derivatives of thiaminase I from *N. gruberi* allegedly lack written description. Applicants respectfully submit that the specification provides adequate description of derivatives of thiaminase. For example, derivatives are described structurally with respect to their homology and length relative to *N. gruberi* thiaminase I (see the specification at page 6, lines 10-22 and page 7, lines 5-14). Given the amino acid sequence of *N. gruberi* thiaminase I presented in Figure 5, the homology and length requirements present in the specification, and the routine nature of amino acid or nucleic acid sequence comparison in the art, one of skill in the art would readily recognize a thiaminase derivative meeting those requirements.

Finally, the Examiner asserts that the claims allegedly lack written description with regard to a non-pathogenic bacterium which comprises a recombinant nucleic acid encoding a thiaminase used in methods of inducing apoptosis in vertebrate cells and methods for delivery (Office Action, pages 9-10, bridging paragraph). Applicant respectfully disagree with the

Examiner's assertion for the reasons described in Section IA. of this paper. Briefly, examples of how a thiaminase can be used in cancer therapy are discussed including cites to the specification of examples of non-pathogenic bacteria which may be used to deliver the thiaminase to a tumor and methods of delivery. Furthermore, one of skill in the art would readily recognize how reports from the literature, both mentioned in the specification and known to those of skill in the art, could be applied to the use of thiaminase-mediated apoptosis in cancer therapy.

For the reasons detailed above, Applicants respectfully submit that the claims are fully supported in the specification and that the written description requirement is fully satisfied. Accordingly, Applicants respectfully request reconsideration and withdrawal of this basis for rejection.

II. 35 U.S.C §112, First Paragraph (Enablement)

A. Claims 1, 3, 11 and 26-31

The rejection of claims 1, 3, 11, and 26-31 under 35 U.S.C §112, first paragraph as allegedly lacking enablement is respectfully traversed. The Examiner asserts that the claimed invention allegedly encompasses gene therapy and that Applicants have provided no guidance on overcoming unpredictabilities of gene therapy (Office Action, page 11). Applicants respectfully submit that the claims do not recite gene therapy.

Gene therapy is known to those of skill in the art as a technique in which a defective gene is replaced with a functioning copy of that gene. The *Encyclopedia Britannica* defines gene therapy as the "introduction of a normal gene into an individual in whom that gene is not functioning, either into those tissue cells that normally express the gene (curing that individual only) or into an early embryonic cell (curing the individual and all future offspring)." Applicants submit that the pending claims in question neither recite the replacement of a defective gene in cells nor the transfection of cells with a gene in order to achieve the desired result of inducing apoptosis in those cells. Withdrawal of the rejections is respectfully requested.

II. 35 U.S.C §112, Second Paragraph

A. Claim 1

The Examiner states that Applicants arguments (Response mailed October 28, 2002) with regard to the rejection of claim 1 under 35 U.S.C §112, second paragraph were considered by the Examiner and found to be persuasive (Office Action, page 13). Applicants acknowledge the reconsideration and withdrawal of the basis for this rejection.

B. Claims 25-27

Claims 25-27 stand rejected under 35 U.S.C §112, second paragraph as being unclear for the recitation in claim 25 of a non-pathogenic bacterium encoding a recombinant nucleic acid sequence encoding a thiaminase. As amended herein, claim 25 recites a "non-pathogenic bacterium comprising a recombinant nucleic acid sequence encoding a thiaminase." This amendment merely corrects a typographical error and makes it consistent with other claims which comprise a "non-pathogenic bacterium comprising a nucleic acid sequence." See, for example, claim 3. Accordingly, Applicants respectfully request reconsideration and withdrawal of the basis for this rejection.

CONCLUSION

In view of the above amendments and remarks, the present application is respectfully submitted to be in condition for allowance. Accordingly, reconsideration and favorable action with respect to the pending claims is respectfully requested. In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the number given below so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date December 16, 2004

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